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Personalized and Precision Medicine in Japan

Hokuto Asano, Government of Japan

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Personalized and Precision Medicine in Japan

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Abstract

As many other countries, Japan is working on development of personalized and precision medicine. This paper explains Japan's policies regarding personalized and precision medicine, including data collection, supports for its development and its insurance coverage such as its process and criteria and describes four drugs and companion diagnosis. Especially as for the insurance coverage, Japan has not examined the cost-effectiveness of personalized and precision medicine and its impact on healthcare expenditures. On the other hand, since the United Kingdom considers cost-effectiveness in considering the insurance coverage, the United Kingdom limits the use of Imatinib due to cost-effectiveness while Japan does not limit it.

1. Introduction

As advanced technologies minimize the involved cost and time, genome analysis is starting to be used for the development of personalized and precision medicine (PPM) and its accompanying diagnostics. Many countries are working to develop PPM. The United States has the Precision Medicine Initiative and Million Veteran Program; the United Kingdom has Genomics England; China, South Korea, and Saudi Arabia have all started their own projects; and Japan is also working to develop PPM. In all these countries, though, the development of PPM may be hampered by insurance questions. Governments may be reluctant to cover PPM and its accompanying tests with public insurance because they are expensive and may increase healthcare expenditures. This paper looks at Japan's PPM policies, as well as the country's experience covering PPM and its companion tests with public insurance. For the sake of comparison, the paper also considers the development of PPM in the United Kingdom.

2. Personalized and Precision Medicine: Strategy

The Japanese government supports the development of PPM, as clearly stated in the Japan Revitalization Strategy 2016 and the Healthcare Policy Strategy. Based on these strategies, the Cabinet Office; the Ministry of Health, Labor and Welfare (MHLW); the Ministry of Education, Culture, Sports, Science, and Technology (MEXT); and the Ministry of Economy, Trade and Industry (METI) have set key performance indicators (KPIs)[1] and worked on PPM-related policies. Similar to the UK Department of Health, which leads Genomics England, MHLW plays a significant role in

[1] KPIs include (1) dramatically improving therapies for lifestyle-related diseases (diabetes, stroke, myocardial infarction, etc.); (2) establishing predictive diagnosis of cancer incidence, and of reactions to and adverse side effects from anticancer drugs; (3) starting clinical research concerning genomic therapy for depression and dementia; and (4) developing innovative methods of diagnosing and treating incurable neuromuscular diseases.

PPM in Japan. MHLW has established a task force for using genome information for medical services and focuses on PPM development, while the Japan Agency for Medical Research and Development (AMED), under MHLW, focuses on PPM research.

In accordance with the accumulated biodata, Japan plans to initially target rare diseases, insurable diseases, cancer, infectious diseases, dementia, undiagnosed diseases, and pharmacogenomics.[2] MHLW is focusing its efforts on PPM for cancer and established a study group for a consortium of genomic medical care for cancer in March 2017. The second target would be lifestyle-related diseases, such as diabetes and circulatory diseases.[3] In addition, according to the KPIs of the Healthcare Policy Strategy, the government will also encourage genomic therapy for depression and dementia. Similarly, the United Kingdom focuses on rare diseases and cancer.[4]

3. Related Policies

The development of PPM heavily depends on the amount of genome data available. Japan is collecting genome data mainly through its three largest biobanks—Bio Bank Japan, Tohoku Medical Megabank, and National Center Bio Bank Network—which work together. Bio Bank Japan, the largest of the three, plans to collect data from 300,000 people. Japan supports clinical trials and clinical research on genomic medical care and plans to select seven core hospitals in 2017 where it will support the provision of genomic medical treatment.[5] In 2016, the total budget for these plans [was ¥11.36 billion ($103 million).[6] The National Cancer Center started the SCRUM-Japan Project, which helps hospitals and pharmaceutical companies develop PPM for cancer. There are no government regulations on genetic testing.

In the United Kingdom, the Department of Health started the 100,000 Genomes Project in 2012, which targeted 70,000 patients in the National Health Service (NHS) who suffer from rare diseases or cancer, along with 30,000 of their family members. The UK government's budget for this initiative was £310 million ($403 million) for the period 2013–17.[7] The size of the United Kingdom's biobank and data collection budget is much larger than that of Japan's. The United Kingdom also established the Genomics England Clinical Interpretation Partnership (which includes clinicians and

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[2] Headquarters for Healthcare Policy, the Cabinet Secretariat. (2017, February 15). Ideas of target diseases for genomic medical care. Retrieved May 20, 2017, from http://www.kantei.go.jp/jp/singi/kenkouiryou/genome/dai7/siryou3_1.pdf.

[3] Ibid.

[4] Koike, A. (2016, January 14). 100,000 Genomes Project. Retrieved June 3, 2017, from https://www.innovationisgreat-jp.com/blog/100000-genomes-project/.

[5] MHLW. (2017, May 29). Draft of Final report of the study group for a consortium of genomic medical care for cancer. Retrieved June 4, 2017, from http://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000166310.pdf.

[6] MHLW. (2016, January 27). Policies related to Genomic medical care. Retrieved May 17, 2017, from http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/160127_task_s1.pdf.

[7] MHLW. (2015, July 15). Other countries' policy on PPM. Retrieved June 4, 2017, from http://www.kantei.go.jp/jp/singi/kenkouiryou/genome/dai4/siryou02.pdf.

researchers) and the Genomics Expert Network for Enterprises (GENE) Consortium (which enables partner companies to access gene data collected under Genomics England and to develop new testing and medication). In 2015, the Precision Medicine Catapult was initiated to accelerate the development of PPM.[8]

4. Insurance Coverage

In Japan, based on the Health Insurance Act, public insurance generally covers medication (see Figure 1). First, the medication's quality, effectiveness, and safety must be approved based on the Law on Securing Quality, Efficacy, and Safety of Products including Pharmaceuticals and Medical Devices, Article 14 (1). To receive public insurance coverage, PPM testing kits and testing equipment also need to be examined. At the same time, drug pricing is decided based on the Director General of Health Insurance Bureau Notification, No. 0210-1, February 10, 2016.[9] The Central Social Insurance Medical Council has the authority to decide whether new medical technology and treatment should be covered by public insurance. Members of this council include insurers, doctors, academics, pharmaceutical companies, and medical equipment companies.

Currently in Japan, cost-effectiveness is not a criterion in decisions regarding which medicines or medical equipment should be covered by public insurance.[10] Although MHLW does test the cost-effectiveness of a few medications, it does not use this criterion when considering whether public insurance can cover PPM testing kits and equipment. However, in the United Kingdom, the National Institute for Health and Care Excellence (NICE) considers the cost-effectiveness of medications to be covered by the national insurance, and therefore restricts the use of some drugs. Among the 169 technology appraisal guidelines published by NICE between 2000 and the end of March 2009, 58 limited the use of drugs and equipment among 169 because of their low cost-effectiveness.[11] Thus, while decision makers in the United Kingdom face an economic obstacle when considering whether PPM should be covered by insurance,[12] their peers in Japan do not.

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[8] Koike, A. (2016, January 14). 100,000 Genomes Project. Retrieved June 3, 2017, from https://www.innovationisgreat-jp.com/blog/100000-genomes-project/.

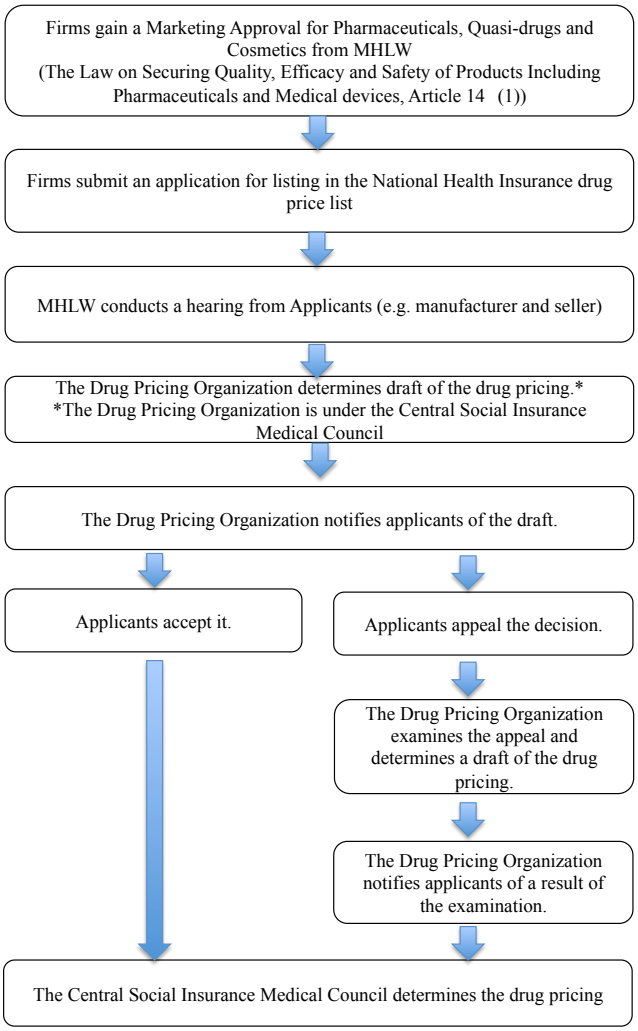
[9] Director General of Health Insurance Bureau,MHLW. (2016, February 10). Stadard of drug price. Retrieved June 8, 2017, from http://www.mhlw.go.jp/file.jsp?id=330790&name=file%2F06-Seisakujouhou-12400000-Hokenkyoku%2F0000112492.pdf.

[10] The task force for using genomic information for medical services, MLHW. (2016, October 28). Concrete measures for development of genomic medical services. Retrieved May 17, 2017, from http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000140440.pdf.

[11] Shiroiwa, T., Fukuda, T., Watanabe, S., & Tsutani, K. (2009). Japanese Journal of Health Economics and Policy. *Japanese Journal of Health Economics and Policy, 21*(2), 155-169.

[12] Davis, J. C., Furstenthal, L., Desai, A., Norris, T., Sutaria, S., Fleming, E., & Ma, P. (2009). The microeconomics of personalized medicine: today's challenge and tomorrow's promise. *Nature Review Drug Discovery, 4*, 279-286.

Figure 1. Process of Considering Insurance Coverage in Japan



Source: Author's compilation.

5. Examples of Approved Drugs and Companion Diagnostics in Clinical Practice

In Japan, cancer was the biggest cause of death over the past decade. Among patients newly diagnosed with cancer, colorectal cancer is the most common, followed by gastric, lung, prostrate, and breast cancers.[13] Since the treatment demands for these are enormous, this paper considered approved drugs and companion diagnostics for these cancers that are already covered by public insurance in Japan (see Table 1). For example, Japan approves Herceptin for patients whose HER2 is excessive. Herceptin, Erbitux, and Gleevec were approved in Japan after being approved in the United States and the European Union. Gefitinib was approved first in Japan and then in the U.S. and EU due to its advanced effectiveness.

[13] National Cancer Center. (2016, July 15th). Cancer Statistics 2015.

Table 1. Examples of Approved Drugs and Companion Diagnostics in Clinical Practice

Drugs	Companion Diagnostic	Target Disease
Herceptin (Trastuzumab)	HER2 genetic specimen preparation	Breast cancer
Erbitux (Cetuximab)	EGRF genetic test	Colorectal cancer
Gleevec (Imatinib)	Amp-CML	Gastrointestinal stromal tumor
Gefitinib (Iressa)	EGRF genetic test	Lung cancer

Table 2. General Information on Approved Drugs

Drugs	Application Date for Public Insurance Coverage	Approval for Public Insurance Coverage	Producer in Japan	Sales
Herceptin (Trastuzumab)[14,15]	January 2001	April 2001 (approved in 1998 in the United States)	Chugai Pharmaceutical Co., Ltd	¥34.1 billion in 2016 ($310 million)
Erbitux (Cetuximab)[16]	January 2007	July 2008 (approved in 2004 in the United States)	Merck Serono Co.	N/A
Gleevec (Imatinib)[17,18]	April 2001	November 2001 (approved in 2001 in the United States)	Novartis Pharmaceuticals Corporation	¥27.5 billion in 2016 ($250 million)
Gefitinib (Iressa)[19]	January 2002	July 2002 (approved in 2003 in the United States)	AstraZeneca Plc	¥20.2 billion in 2013 ($184 million)

Table 3 shows the price of approved drugs in Japan and the United Kingdom, which are quite expensive. For example, the monthly expenditure of patients who have to take just one Gefitinib a day is more than ¥180,000 ($1,636), and for those who have to take 400 milligrams (mg) of Gleevec every day, it is more than ¥295,860 ($2,688). Among people 70 years and under, the copayment rate is 30 percent; for those who are 70 to 74 years old it is 20 percent; and for those above 74 years it is 10 percent. Thus, people do not pay the exact same amount. In addition, Japan has a High-Cost Medical Expense Benefit that has established a cap on the drug expenditures of the insured. Except for Gefitinib, drug prices in Japan are more expensive than those in the United Kingdom. These results are similar to that of another research study that showed the average price of a new drug in

[14] Chugai Pharmaceutical Co., Ltd. (2016, December). Herceptin. Retrieved June 3, 2017, from https://chugai-pharm.jp/hc/ss/pr/drug/her_via0060_01/if/PDF/her_if.pdf?_back=6,1
Medication Interview Form.
[15] Chugai Pharmaceutical Co., Ltd. (2016, December). Sales in 2016. Retrieved June 3, 2017, from https://www.chugai-pharm.co.jp/ir/finance/revenue_product.html.
[16] Merck Serono Co. (2015, May). Erbitax Injection. Retrieved June 3, 2017, from http://www.info.pmda.go.jp/go/interview/1/380079_4291415A1021_1_003_1F
Medication Interview Form.
[17] Novartis Pharmaceuticals Corporation. (2016, August). Glivec Tablets 100mg. Retrieved June 3, 2017, from https://drs-net.novartis.co.jp/SysSiteAssets/common/pdf/gli/if/if_gli.pdf
Medication Interview Form.
[18] Novartis Pharmaceuticals Corporation. (2016, December). Performances in 2016. Retrieved June 3, 2017, from https://www.novartis.co.jp/news/press-room/year-results.
[19] AstraZeneca plc. (2010, November). Iressa Tablets 250. Retrieved June 3, 2017, from http://i250-higainokai.com/2010-11-iressa_if.pdf
Medication Interview Form.

Japan as 108–204 percent higher than that of the United Kingdom, depending on the exchange rate.[20]

Furthermore, although both Japan and the United Kingdom have approved Imatinib, the United Kingdom limits its use because of cost-effectiveness.[21] One of NICE's guidelines states that an increase in the dose of Imatinib is not recommended for people unresponsive to treatment or for people who develop a progressive disease.[22]

Table 3. Price of Approved Drugs in Japan and the United Kingdom

Drugs	Japan (from March 17, 2017)[23,24]	United Kingdom[25]
Herceptin (Trastuzumab)	¥24,469/60 mg ($3.7/1 mg)	£407.40/150 mg[26] ($3.5/1 mg)
Erbitux (Cetuximab)	¥36,920/20 ml (100 mg) ($3.4/1 mg)	£178.10/20 ml (100 mg)[27] ($2.3/1 mg)
Gleevec (Imatinib)	¥2,465.5/1 capsule (100 mg/1 capsule) ($22.4/1 capsule)	£1,442.01/120 capsules (100 mg/1 capsule)[28] ($15.6/1 capsule)
Gefitinib (Iressa)	¥6,712.7/1 tablet (250 mg/1 tablet) ($61/1 tablet)	£2,167.71/30 tablets (250 mg)[29] ($93.8/1 tablet)

When we compare Tables 2 and 4 we observe a time lag between the approval of drugs and the approval of the companion diagnostics. For example, although Herceptin was approved in April

[20] MHLW. (2013, February 27). Comparison on price of new drugs with European countries. Retrieved June 4, 2017, from http://www.mhlw.go.jp/stf/shingi/2r9852000002w6r3-att/2r9852000002w6uj.pdf.

[21] Shiroiwa, T., Fukuda, T., Watanabe, S., & Tsutani, K. (2009). Japanese Journal of Health Economics and Policy. *Japanese Journal of Health Economics and Policy, 21*(2), 155-169.

[22] NICE. (2004, October 27). Imatinib for the treatment of unresectable and/or metastatic gastro-intestinal stromal tumours. Retrieved June 4, 2017, from https://www.nice.org.uk/guidance/ta86/documents/appraisal-consultation-document-imatinib-for-the-treatment-of-unresectable-andor-metastatic-gastrointestinal-stromal-tumours.

[23] MLHW. (2017, March 17). Listing in the National Health Insurance drug price list (Apply from March 17, 2017). Retrieved May 17, 2017, from http://www.mhlw.go.jp/topics/2016/04/tp20160401-01.html.

[24] $1 = ¥110.

[25] $1 = £0.77.

[26] NICE. (n.d.). Herceptin® (Roche) Report adverse reaction(s). Retrieved June 4, 2017, from https://www.evidence.nhs.uk/formulary/bnf/current/8-malignant-disease-and-immunosuppression/81-cytotoxic-drugs/815-other-antineoplastic-drugs/trastuzumab/trastuzumab/herceptin.

[27] NICE. (2015, January 25). Cetuximab, bevacizumab, and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy), and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy. Retrieved June 4, 2017, from https://www.nice.org.uk/guidance/ta242/chapter/3-the-technologies.

[28] Novartis Korea Ltd. (2001, December). Application for Reimbursement Price Adjustment in Korea. Retrieved June 4, 2017, from http://www.cptech.org/ip/health/gleevec/7prices.pdf.

[29] NICE. (2014, August 7). Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy. Retrieved June 4, 2017, from https://www.nice.org.uk/guidance/ta374/documents/erlotinib-and-gefitinib-for-treating-nonsmallcell-lung-cancer-that-has-progressed-following-prior-chemotherapy-review-of-ta162-and-ta175-appraisal-consultation-document.

2001, the HER2 genetic specimen preparation was approved only in April 2010. Hence, between April 2001 and March 2010, the HER2 genetic specimen preparation tests conducted by medical institutions were not covered by public insurance. According to a research study,[30] due to this time lag physicians did not have accurate information on which to base decisions regarding treatments, and this also decreased the chances of physicians adopting a new therapeutic-diagnostic approach. In July 2000, soon after Herceptin was approved, the Japanese Society of Pathology published guidelines for an HER2 examination for breast cancer to provide physicians with accurate information.

Table 4. Approval Date and Cost of Companion Diagnostics

Diagnostics	Approval Date[31]	Cost (from March 17, 2017)[32]
HER2 genetic specimen preparation	April 2010	¥27,000 ($245)
EGRF genetic test for colorectal cancer	April 2010	¥36,920/100 mg (20 ml) ($336)
Amp-CML	TMA method: November 2004 Real-time RT-PCR method: April 2015	TMA method: ¥12,000 ($109). Real-time RT-PCR method: ¥25,200 ($229)
EGRF genetic test for lung cancer	April 2006	PCR method: ¥25,000 ($227) Non-PCR method: ¥21,000 ($191)

6. Other Genetic Testing

Japan's public insurance also covers the genetic testing mentioned in Table 5.

Table 5. Tests and Their Costs

Test	Price	Note
Genetic testing for targeted 72 diseases	¥38,800 ($353)	Purpose is to figure out hereditary disease. In principle, hospitals or clinics can claim the fee of this testing through public insurance only once for each patient.
12 tissue examinations for cancer	¥21,000–¥65,200 (depending on the test) ($191–$593)	Purpose is to figure out a method of treating and conducting a precise pathological diagnosis.
Hematopoietic tumor genetic testing	¥21,000 ($191)	Purpose is to figure out a method of treating leukemia patients.
Polymorphism of UGT1A1 gene	¥21,000 ($191)	Purpose is to figure out the dose amount of irinotecan hydrochloride (anti-cancer drug). Irinotecan hydrochloride is for lung-cancer and metastatic-colorectal-cancer patients.

Coverage of the above tests has been expanded. Since MHLW needs to financially support patients who suffer from incurable diseases based on the Act on Medical Care for Rare Disease

[30] Hamburg, M. A., & Collins, F. S. (2010). The Path to Personalized Medicine. *The New England Journal of Medicine, 363*(4), 301-304.
[31] LSI Medience Corporation. (2013, July 13th). Molecular Target Drug and Clinical Examination. Retrieved June 3, 2017, from http://www.aichi-amt.or.jp/labo/patho/reco/20130713_01.pdf.
[32] MLHW. (2017, March 17). Listing in the National Health Insurance drug price list (Apply from March 17, 2017)). Retrieved May 17, 2017, from http://www.mhlw.go.jp/topics/2016/04/tp20160401-01.html.

Patients enacted in 2015, it transformed genetic testing for the targeted 34 diseases to genetic testing for the targeted 72 diseases in 2015.[33] Also, in 2017, RET gene testing for medullary thyroid cancer and RB1 gene testing for omentum swollen bud cells were included in genetic testing for the targeted 72 diseases. In addition to the above, genetic counseling is also covered by public insurance and costs ¥5,000 ($45).

Japan's public insurance, however, does not cover some genetic testing such as BRCA1/2 genetic testing for breast cancer due to several reasons such as insufficient patient data.

7. Conclusion

The Japanese government has not examined the cost-effectiveness of PPM and its impact on healthcare expenditures. One research study examined the cost-effectiveness of Gefitinib and epidermal growth factor receptor (EGFR) testing in Japan by calculating the incremental cost-effectiveness ratio and showing that this combination was more cost-effective than treatment without EGFR testing.[34] Japan currently covers companion genetic tests. Furthermore, for cancer-related genetic testing, Japan is considering whether public insurance should cover genetic panel testing, which does not specify the target molecule but rather examines multiple genes at the same time.[35] In addition, Japan plans to approve PPM that has been proven effective and safe under certain conditions. However, policies to promote PPM may increase total healthcare expenditures. Since Japan already has extensive public debt and its healthcare expenditures are expected to increase due to its aging population, the Japanese government must consider cost-effectiveness when determining public insurance coverage for PPM.

[33] MHLW. (2016, February 18). The 5th meeting of the task force for using genomic information for medical services. Retrieved June 8, 2017, from http://www.mhlw.go.jp/file/05-Shingikai-10601000-Daijinkanboukouseikagakuka-Kouseikagakuka/0000125748.pdf.

[34] Narita, Y., Matsushima, Y., Shiroiwa, T., Chiba, K., Nakanishi, Y., Kurokawa, T., & Urushihara, H. (2015). Cost-effectiveness analysis of EGFR mutation testing and Gefitinib as first-line therapy for non-small cell lung cancer. *Lung Cancer, 90*, 71-77.

[35] MHLW. (2017, May 29). Draft of final report of the study group for a consortium of genomic medical care for cancer. Retrieved June 4, 2017, from http://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000166310.pdf.